Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplemental Materials:

Influenza vaccine effectiveness in the United States — 2015/16 season

Contents

Acknowledgements

Supplemental Methods

Defining high-risk conditions

We used International Classification of Diseases (ICD) codes assigned to medical encounters in the year prior to enrollment to define the presence/absence of medical conditions that may increase the risk of severe influenza disease. ICD version 9 was used for encounters prior to October 2015, and ICD version 10 for encounters on or after October 1 2015.

Table: ICD codes used to define high-risk medical conditions. Listed codes include all subcodes

Disease category	ICD-9 codes	ICD-10 codes
Chronic cardiac diseases and circulatory diseases	093, 391, 393-398, 402, 404, 410-414, 416, 417, 423-426, 427.1-427.8, 428, 429, 440-444, 446, 447, 745, 746.9, 747, V42.1, V45.0, V45.81, V45.82	A52.0, I01, I02, I05-I09, I11, I13, I20-I28, I31, I33-I44, I46, I48, I50-I52, I71-I76, I79, I81-I82, I85, I97.0, I97,1, M31, Q20-Q28, Q89.3, R00.1, Z94.1, Z95, Z98.61
Chronic pulmonary diseases	011, 012, 031.0, 135, 277.0, 277.6, 491-496, 500-506, 508, 514-517, 518.1-518.3, 518.6, 518.83, 519.0, 748.4,-748.6, 759.3, 770.2, 770.7, V42.6	A15, A31.0, B39-B41, B44, B45, B46.0, D86.0, E84, E88.01, J18.2, J41-J45, J47, J60-J70, J80-J82, J84-J86, J95.0, J96, J98.1, J99, P25-P28, Q33, T86.3, T86.8, Z94.2
Diabetes mellitus	250, 251, 648.0, 357.2, 362.0, 362.11, 36.41	E08-E11, E13, O24
Chronic renal disease	403, 581-583, 585-587, 588.0, 588.1, 590.0, V42.0, V45.1, V56	I12, N01-N08, N11, N14-N18, N25, N26, N28, Q27.1, Q27.2, Q60, Z49, Z91.15, Z94.0, Z99.2
Hemoglobinopathies	282-284	D55, D56.0-D56.2, D56.4, D56.5, D56.9, D57.0- D57.2, D57.4, D57.8, D58-D61, D64.0-D64.4, D64.8, D65-D68
Immunosuppressive disorders	042, 136.3, 279, 288.0, 288.1, 288.2, 288.4, 446, 710.0, 710.1, 710.2, 710.3, 710.4, 714, V08, V42.2, V42.7, V42.8, V42.9, V42.1, V42.6, V42.0, V58.0, V58.1	B20, B59, B97.3, D47.Z1, D70-D73, D76, D80-D84, D89, M05-M08, M30-M34, M35.0, M35.9, Q89.0, T45.1X1, Z21, Z48.2, Z51.0, Z51.1, Z94
Malignancy	140-172, 174-208	C00-C26, C30-C34, C37-C41, C43-C58, C60-C86, C88, C90-C96, C4A, C7A, C7B, D03, D46, Z85
Metabolic diseases, excluding diabetes	255, 270, 271, 277	E70-E72, E74, E75.2, E76-E80, E83, E85, E88, E89.1, E89.6

Liver diseases	571, 572.2-572.8	B18, K70-K77
Neurological/Musculoskeletal	290, 294.1, 318.1, 318.2, 330-332, 333.0, 333.4-333.9, 334-336, 340-343, 344.0, 358.0, 358.1, 359, 756.1, 756.3-756.6, 768.5, 780.72	H49.81, M12.0, M30, M36.0, A17.0, E75.02, E75.19, E75.4, F01-F03, F71-F73, F84.2, G10-G14, G20, G21, G23-G26, G30-G32, G35-G37, G40, G45, G46, G60-G64, G70, G71, G73, G80-G83, G90.3, G91, G93, G94, G95, G99.2, P91, Q00-Q07, Q76, Q77-Q79, Q85, Q87.4, Q90-Q93, Q96, R41, R53.2, R54
Cerebrovascular disease	431-434, 437, 438	I60-I63, I68, I69
Morbid obesity	278.01	E66.01, E66.2, Z68.4
Endocrine disorders		E00, E01, E03, E05, E06, E15, E16, E20-E29, E31, E32, E34

Influenza vaccination history

As mentioned in the main manuscript, virus strains recommended for 2015/16 northern hemisphere influenza vaccines were A/California/7/2009 (H1N1pdm09)-like, A/Switzerland/9715293/2013 (H3N2)-like, B/Phuket/3073/2013-like (Yamagata lineage) viruses, and (for quadrivalent vaccines), B/Brisbane/60/2008-like virus (Victoria lineage). The A/Switzerland/9715293/2013-like virus belongs to genetic clade 3C.3a. B/Phuket/3073/2013-like virus belongs to genetic group 3, and B/Brisbane/60/2008-like virus to genetic group 1A. A(H1N1)pdm09 viruses isolated prior to 2011 have not been assigned to genetic groups.

For our primary analyses, we defined influenza vaccination history from a combination of Electronic Immunization Records (EIRs) and self- or parent-reported vaccination data. EIRs included electronic health records from enrollment clinics, employee health records, and state immunization registries. Data extracted from EIRs included vaccine type, date of vaccination, and (where available) lot number, manufacturer, and route of administration. If not specifically available, vaccine type (including LAIV and trivalent/quadrivalent inactivated vaccines, IIV3/IIV4) was derived from manufacturer, lot number, and route of administration. At the all study sites, subjects were considered vaccinated if they had an EIR-documented record of influenza vaccination 14 or more days prior to illness onset. Subjects without EIR-documented vaccination were handled somewhat differently at the study sites, depending on access to and expected completeness of EIR data:

- Wisconsin site: EIR data come from the Registry for Effectively Communicating Immunization Needs (RECIN). This registry combines immunization records from all Marshfield Clinic providers and the Wisconsin Immunization Information System (IIS).

Validity of the RECIN registry has been previously demonstrated.[1] EIR data are assumed to be complete for subjects of all ages, so subjects without EIR-documented vaccination were assumed to be unvaccinated.

- Washington site: EIR data come from Kaiser Permanente Washington's Immunization Registry, which combines data from all Kaiser Permanente Washington providers and the Washington IIS. EIR data are assumed to be complete for children <18 years of age, but vaccinations given to adults at workplaces may be missing from EIR sources.[2] Consistent with sites other than Wisconsin, subjects aged <9 years of age without EIR-documented vaccination were assumed to unvaccinated. Subjects aged ≥9 years who self-reported vaccination (or had parental self-report of vaccination) at enrollment but for whom EIR documentation was not available were contacted by phone and asked for additional data on influenza vaccination. Subjects aged ≥9 years who provided a plausible vaccination provider and an approximate date of vaccination (termed "plausible self-report") were considered vaccinated; subjects aged ≥9 years not providing a plausible self-report, or who self-reported being unvaccinated in this verification step were assumed to be unvaccinated.

- Michigan site: EIR data come from the University of Michigan and Henry Ford electronic medical records (EMRs) and from the Michigan IIS (Michigan Care Improvement Registry). Subjects with EIR-documented vaccination were assumed to be vaccinated, as were subjects aged ≥9 years with plausible self-report (or plausible parent report) of influenza vaccination at the enrollment interview. Other subjects were considered unvaccinated.

- Texas site: EIR data come from multiple sources, including the Baylor Scott & White electronic medical record, Scott & White Health Plan claims databases, Baylor Scott & White employee immunization records, primary care provider records, retail pharmacies, and the Texas IIS (ImmTrac), an opt-in registry. Subjects with EIR-documented vaccination were assumed to be vaccinated, as were subjects aged ≥9 years with plausible self-report (or plausible parent report) of influenza vaccination at the enrollment interview. Other subjects were considered unvaccinated.

- Pennsylvania site: EIR data come from the University of Pittsburgh Medical Center (UPMC) electronic medical record, UPMC employee vaccination records, Highmark and UPMC claims databases, primary care provider records, and the Pennsylvania IIS. Details on vaccine provider and approximate date of vaccination were collected during enrollment interviews. Subjects with EIR-documented vaccination were assumed to be vaccinated, as were subjects aged ≥9 years with plausible self-report (or plausible parent report) of influenza vaccination at the enrollment interview. Other subjects were considered unvaccinated.

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[1] Irving SA, Donohue JG, Shay DK, Ellis-Coyle TL, Belongia EA. "Evaluation of self-reported and registry-based influenza vaccination status in a Wisconsin cohort." *Vaccine* 2009; 27(47):6546-9

[2] Centers for Disease Control Prevention. "Progress in immunization information systems - United States, 2012." *MMWR Morb Mort Wkly Rep*; 2013;62:1005-8.

At the Wisconsin site, vaccine type (inactived vs. live attenuated) was defined from EIR data only. At all other sites, vaccine type was defined from EIR data if vaccine type was available in the EIR (3,148 subjects), or by self-reported vaccine type otherwise (234 subjects). Subjects aged ≥50 years without EIR-documented vaccine type were assumed to have received inactivated vaccine (14 subjects).

Laboratory testing

Respiratory specimens (combined nasal and oropharyngeal swabs for subjects aged ≥2 years, nasal swabs for subjects aged <2 years) were collected from all study subjects. Specimens were collected for research purposes only and are independent of any specimens collected for clinical testing. Thus, the decision to test for influenza was not subject to a provider's discretion. Specimens were tested for influenza via real time reverse transcriptase polymerase chain reaction (RT-PCR) at each of the study sites. The exception was the Washington site; specimens from subjects enrolled at the Washington site were frozen at -70 $^{\circ}$C and shipped to the Wisconsin site for testing. RT-PCR testing followed a common protocol across all study sites using probes and primers provided by the Centers for Disease Control and Prevention (CDC).

Analysis
- Missing data: As indicated in Table 1, we had complete data on exposure, outcome, and covariates for the final adjusted model (age, study site, high-risk status, and illness onset). Among other potential confounders examined, missing data were uncommon (Table 1). Body mass index (BMI) had the greatest proportion of subjects with missing data (2%). When assessing these covariates as potential confounders in multivariable models, observations with missing values for these covariates were excluded.
- Model fit: We used the Hosmer-Lemeshow statistic as a measure of goodness of fit. The Hosmer-Lemeshow test statistic was not significant in either the final adjusted model presented in the main paper (p=0.08) or the comparison-adjusted model presented in supplemental materials (p=0.51) indicating there was not enough evidence to indicate the models had lack of fit.
- Sample size: Sample size was chosen in order to estimate VE with reasonable precision (+/- 15%) overall and to detect statistically significant VE within pre-defined age groups. Each study site was required to enroll at least 800 subjects per season, with at least 200 in each of the following age groups: 6 months to 18 years, 19 to 49 years, and ≥50 years. Assuming that 25% of subjects would test positive for influenza, assuming 40% of subjects would vaccinated, and assuming a true VE of 50%, this sample size would enable estimation of a VE of 50% (95% CI, 35% to 66%) with type I error rate of 0.05. It would also give us at least

80% power to reject the null hypothesis of no VE in each of the pre-defined age group with type I error rate of 0.05.

Supplemental Figure: Enrolled subjects, stratified by onset week and influenza test results
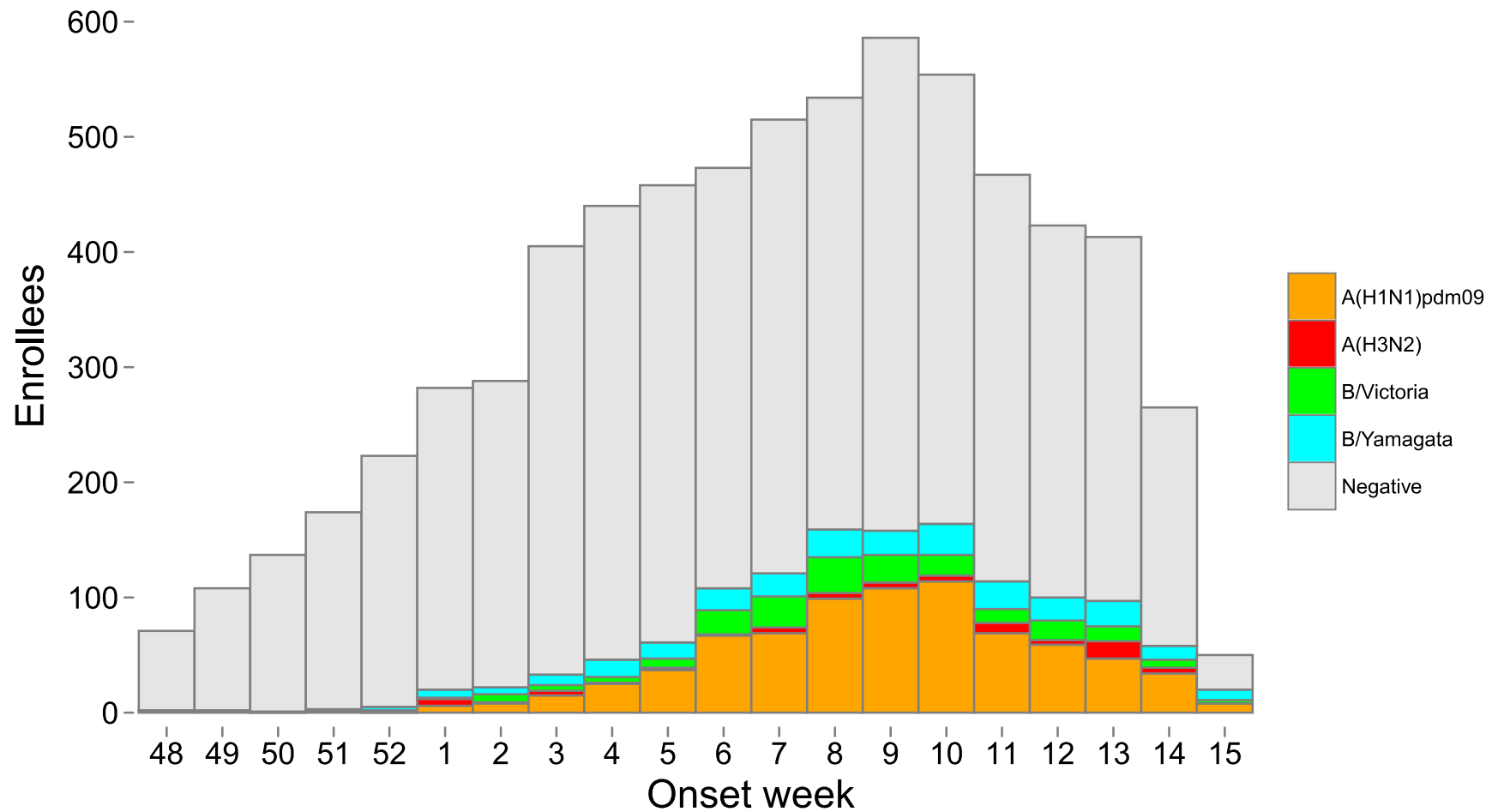
Supplemental Table 1

Descriptive characteristics of study participants with medically attended acute respiratory illness, by lab-confirmed influenza virus infection status. Numbers are counts (column percentage) unless otherwise indicated

Characteristic	Influenza negative (N=5570)	Influenza positive (N=1309)	Influenza A(H1N1)pdm09 (N=768)	Influenza A(H3N2) (N=72)	Influenza B/Yamagata (N=253)	Influenza B/Victoria (N=200)
Age						
<9 years	1,272 (23%)	254 (19%)	160 (21%)	6 (8%)	34 (13%)	55 (28%)
9-17 years	694 (12%)	164 (13%)	51 (7%)	6 (8%)	37 (15%)	70 (35%)
18-49 years	1,957 (35%)	499 (38%)	311 (40%)	34 (47%)	91 (36%)	52 (26%)
50-64 years	918 (16%)	283 (22%)	194 (25%)	13 (18%)	64 (25%)	8 (4%)
≥65 years	729 (13%)	109 (8%)	52 (7%)	13 (18%)	27 (11%)	15 (8%)
Male sex	2,236 (40%)	597 (46%)	346 (45%)	32 (44%)	119 (47%)	95 (48%)
Study site						
Michigan	751 (13%)	243 (19%)	181 (24%)	10 (14%)	23 (9%)	30 (15%)
Pennsylvania	1,254 (23%)	356 (27%)	252 (33%)	8 (11%)	60 (24%)	31 (16%)
Texas	1,147 (21%)	192 (15%)	54 (7%)	17 (24%)	31 (12%)	89 (45%)
Washington	1,399 (25%)	321 (25%)	97 (13%)	37 (51%)	129 (51%)	49 (25%)
Wisconsin	1,019 (18%)	197 (15%)	184 (24%)	(0%)	10 (4%)	1 (1%)
Race/ethnicity						
White, non-Hispanic	4,233 (76%)	919 (70%)	567 (74%)	52 (72%)	175 (69%)	111 (56%)
Black, non-Hispanic	402 (7%)	157 (12%)	101 (13%)	4 (6%)	25 (10%)	25 (13%)
Other, non-Hispanic	456 (8%)	132 (10%)	60 (8%)	10 (14%)	32 (13%)	30 (15%)
Hispanic	455 (8%)	98 (7%)	38 (5%)	6 (8%)	20 (8%)	34 (17%)
Unknown	24 (0%)	3 (0%)	2 (0%)	(0%)	1 (0%)	(0%)
Body Mass Index*						
<18.5	34 (1%)	8 (1%)	5 (1%)	1 (2%)	(0%)	2 (3%)
18.5–24.9	838 (23%)	238 (27%)	144 (26%)	18 (30%)	49 (27%)	20 (27%)

25–29.9	984 (27%)	271 (30%)	168 (30%)	21 (35%)	56 (31%)	20 (27%)
30–30.9	1,246 (35%)	266 (30%)	165 (30%)	17 (28%)	60 (33%)	22 (29%)
≥40	440 (12%)	88 (10%)	64 (11%)	3 (5%)	11 (6%)	8 (11%)
Unknown	62 (2%)	20 (2%)	11 (2%)	(0%)	6 (3%)	3 (4%)
Any high-risk condition†	2,137 (38%)	439 (34%)	270 (35%)	30 (42%)	89 (35%)	40 (20%)
Asthma/pulmonary high-risk condition	1,086 (19%)	204 (16%)	121 (16%)	13 (18%)	41 (16%)	26 (13%)
Cardiovascular high-risk condition	618 (11%)	104 (8%)	66 (9%)	5 (7%)	21 (8%)	9 (5%)
Diabetes high-risk condition	422 (8%)	79 (6%)	57 (7%)	3 (4%)	12 (5%)	6 (3%)
BMI ≥40	308 (6%)	58 (4%)	44 (6%)	2 (3%)	7 (3%)	5 (3%)
Other high-risk condition	1,097 (20%)	229 (17%)	151 (20%)	16 (22%)	43 (17%)	13 (7%)
General health status						
Excellent	1,783 (32%)	488 (37%)	272 (35%)	22 (31%)	94 (37%)	94 (47%)
Very good	2,048 (37%)	483 (37%)	290 (38%)	23 (32%)	94 (37%)	72 (36%)
Good	1,348 (24%)	267 (20%)	159 (21%)	20 (28%)	53 (21%)	28 (14%)
Fair/Poor	387 (7%)	70 (5%)	45 (6%)	7 (10%)	12 (5%)	6 (3%)
Missing	4 (0%)	1 (0%)	1 (0%)	(0%)	(0%)	(0%)
Smoker	490 (9%)	103 (8%)	79 (10%)	3 (4%)	11 (4%)	7 (4%)
Exposure to smoke	1,121 (20%)	223 (17%)	140 (18%)	9 (13%)	33 (13%)	40 (20%)
Interval from onset to enrollment						
<3 days	1,540 (28%)	525 (40%)	351 (46%)	29 (40%)	64 (25%)	77 (39%)
3–4 days	2,176 (39%)	516 (39%)	287 (37%)	28 (39%)	110 (43%)	87 (44%)
5–7 days	1,854 (33%)	268 (20%)	130 (17%)	15 (21%)	79 (31%)	36 (18%)
Current health assessment (median, interquartile range)‡	60 (45-75)	50 (35-70)	50 (30-65)	50 (35-65)	50 (40-70)	50 (40-70)
Education						

Less than high school graduate	219 (4%)	28 (2%)	15 (2%)	(0%)	3 (1%)	10 (5%)
Graduated high school (or obtained GED)	1,126 (20%)	241 (18%)	163 (21%)	12 (17%)	36 (14%)	28 (14%)
Some college (including vocational training, associate's degree)	2,061 (37%)	478 (37%)	282 (37%)	30 (42%)	90 (36%)	72 (36%)
Bachelor's degree	1,234 (22%)	324 (25%)	182 (24%)	15 (21%)	69 (27%)	56 (28%)
Advanced degree	914 (16%)	235 (18%)	125 (16%)	15 (21%)	54 (21%)	33 (17%)
Unknown	16 (0%)	3 (0%)	1 (0%)	(0%)	1 (0%)	1 (1%)
Vaccinated	2,902 (52%)	494 (38%)	308 (40%)	30 (42%)	91 (36%)	59 (30%)

* BMI was calculated as kg/m^2 from height and weight recorded in electronic health records, for adults ≥18 years of age only

†Presence of high-risk health conditions were defined as the presence of ≥1 medical record-documented high risk code (ICD-9 prior to 10/1/2015, ICD-10 subsequently) in the year prior to enrollment

‡Current health assessment was missing for 5 influenza negatives, 2 B/Yamagata positive cases, and 1 B/Victoria positive case

Supplemental Table 2

Crude and adjusted estimates of influenza vaccine effectiveness, overall and stratified by age group, vaccine type, and virus type/subtype/lineage

Influenza (sub)type/Age group/Vaccine type	Influenza Positive Vaccinated/Total	(%)	Influenza Negative Vaccinated/Total	(%)	Crude (%)	Crude (95% CI)	Adjusted* VE %	Adjusted* 95% CI
Influenza A and B								
Any vaccine								
Overall	494/1309	37.7	2902/5570	52.1	44%	(37 to 51)	48%	(41 to 55)
6 months - 8 years	87/254	34.3	630/1272	49.5	47%	(30 to 60)	51%	(33 to 64)
2-8 years	75/228	32.9	436/961	45.4	41%	(20 to 56)	48%	(27 to 63)
2-17 years	108/392	27.6	713/1655	43.1	50%	(36 to 61)	52%	(38 to 63)
9-17 years	33/164	20.1	277/694	39.9	62%	(43 to 75)	59%	(36 to 74)
18-49 years	146/499	29.3	841/1957	43.0	45%	(32 to 56)	52%	(39 to 61)
50-64 years	150/283	53.0	562/918	61.2	29%	(7 to 45)	26%	(2 to 44)
≥65 years	78/109	71.6	592/729	81.2	42%	(8 to 63)	42%	(6 to 64)
By study site								
Michigan	118/243	48.6	421/751	56.1	26%	(1 to 45)	29%	(2 to 49)
Pennsylvania	126/356	35.4	602/1254	48	41%	(24 to 53)	42%	(23 to 56)
Texas	52/192	27.1	503/1147	43.9	52%	(33 to 66)	50%	(28 to 66)
Washington	116/321	36.1	820/1399	58.6	60%	(49 to 69)	64%	(52 to 73)
Wisconsin	82/197	41.6	556/1019	54.6	41%	(19 to 56)	46%	(24 to 62)
Any inactivated vaccine (IIV)								
Overall	456/1271	35.9	2779/5447	51.0	46%	(39 to 53)	51%	(44 to 57)
6 months - 8 years	62/229	27.1	564/1206	46.8	58%	(42 to 69)	59%	(42 to 71)
2-8 years	50/203	24.5	370/895	41.3	54%	(34 to 67)	56%	(37 to 70)

2-17 years	73/357	20.5	609/1551	39.3	60%	(48 to 70)	60%	(47 to 70)
9-17 years	23/154	14.9	239/656	36.4	69%	(51 to 81)	66%	(44 to 80)
18-49 years	143/496	28.8	822/1938	42.4	45%	(32 to 56)	52%	(39 to 62)
50-64 years	150/283	53.0	562/918	61.2	29%	(7 to 45)	26%	(2 to 44)
≥65 years	78/109	71.6	592/729	81.2	42%	(8 to 63)	42%	(6 to 64)
IIV3 only†								
Overall	140/955	14.7	850/3518	24.2	46%	(24 to 56)	41%	(25 to 53)
6 months - 17 years	19/317	6.0	218/1277	17.1	69%	(50 to 81)	56%	(22 to 75)
18-49 years	29/382	7.6	149/1265	11.8	38%	(7 to 59)	38%	(1 to 61)
50-64 years	47/180	26.1	121/477	25.4	-4%	(-54 to 30)	-5%	(-68 to 34)
≥65 years	45/76	59.2	362/499	72.6	45%	(10 to 67)	42%	(0 to 66)
IIV3 SD only								
Overall	110/925	11.9	671/3339	20.1	46%	(33 to 57)	41%	(24 to 54)
≥65 years	15/46	32.6	186/323	57.6	64%	(31 to 81)	68%	(30 to 85)
IIV3 HD only								
≥65 years	30/61	49.2	176/313	56.2	25%	(-30 to 57)	11%	(-70 to 54)
IIV4 only								
Overall	257/1072	24.0	1628/4296	37.9	48%	(40 to 56)	54%	(45 to 61)
6 months - 8 years	45/212	21.2	399/1041	38.3	57%	(38 to 70)	61%	(41 to 73)
9-17 years	18/149	12.1	158/575	27.5	64%	(39 to 79)	67%	(41 to 81)
18-49 years	86/439	19.6	535/1651	32.4	49%	(34 to 61)	56%	(41 to 67)
50-64 years	79/212	37.3	348/704	49.4	39%	(17 to 56)	33%	(6 to 53)
≥65 years	29/60	48.3	188/325	57.9	32%	(-18 to 61)	24%	(-44 to 60)
Live attenuated influenza vaccine (LAIV4) only								
Overall (2-49 y)	37/674	5.5	107/2165	4.9	-12%	(-64 to 24)	4%	(-47 to 37)
2 years - 17 years	35/319	11	101/1043	9.7	-15%	(-73 to 23)	5%	(-47 to 39)

2 years - 8 years	25/178	14.0	63/588	10.7	-36%	(-124 to 17)	0%	(-75 to 43)
9-17 years	10/141	7.1	38/455	8.4	16%	(-72 to 59)	17%	(-84 to 63)

Influenza A(H1N1pdm09)

Any vaccine

Overall	308/768	40.1	2902/5570	52.1	38%	(28 to 47)	45%	(34 to 53)
6 months - 8 years	58/160	36.3	630/1272	49.5	42%	(19 to 59)	49%	(26 to 65)
2-8 years	47/139	33.8	436/961	45.4	38%	(11 to 58)	48%	(22 to 65)
2-17 years	58/190	30.5	713/1655	43.1	42%	(20 to 58)	53%	(33 to 67)
9-17 years	11/51	21.6	277/694	39.9	59%	(18 to 79)	63%	(22 to 82)
18-49 years	98/311	31.5	841/1957	43.0	39%	(21 to 53)	46%	(29 to 59)
50-64 years	110/194	56.7	562/918	61.2	17%	(-13 to 39)	10%	(-26 to 36)
≥65 years	31/52	59.6	592/729	81.2	66%	(39 to 81)	66%	(36 to 81)

Any IIV

Overall	286/746	38.3	2779/5447	51.0	40%	(30 to 49)	47%	(37 to 56)
6 months - 8 years	41/143	28.7	564/1206	46.8	54%	(33 to 69)	59%	(38 to 73)
2-8 years	30/122	24.6	370/895	41.3	54%	(29 to 70)	59%	(36 to 74)
2-17 years	38/170	22.4	609/1551	39.3	55%	(35 to 69)	63%	(45 to 75)
9-17 years	8/48	16.7	239/656	36.4	65%	(24 to 84)	68%	(27 to 86)
18-49 years	96/309	31.1	822/1938	42.4	39%	(21 to 53)	46%	(29 to 59)
50-64 years	110/194	56.7	562/918	61.2	17%	(-13 to 39)	10%	(-26 to 36)
≥65 years	31/52	59.6	592/729	81.2	66%	(39 to 81)	66%	(36 to 81)

IIV3 only

Overall	99/559	17.7	850/3518	24.2	32%	(15 to 46)	45%	(28 to 58)
6 months - 17 years	15/157	9.6	218/1277	17.1	49%	(11 to 70)	64%	(32 to 81)
18-49 years	23/236	9.8	149/1265	11.8	19%	(-28 to 49)	37%	(-7 to 62)
50-64 years	40/124	32.3	121/477	25.4	-40%	(-115 to 9)	-5%	(-76 to 38)
≥65 years	21/42	50.0	362/499	72.6	62%	(29 to 80)	62%	(24 to 81)

IIV3 SD only								
Overall								
≥65 years	9/30	30.0	186/323	57.6	68%	(29 to 86)	76%	(38 to 90)
IIV3 HD only								
≥65 years	12/33	36.4	176/313	56.2	56%	(6 to 79)	42%	(-40 to 76)
IIV4 only								
Overall	150/610	24.6	1628/4296	37.9	47%	(35 to 56)	49%	(37 to 59)
6 months - 17 years	33/175	18.9	557/1616	34.5	56%	(35 to 70)	60%	(38 to 74)
18-49 years	55/268	20.5	535/1654	32.4	46%	(26 to 61)	49%	(28 to 64)
50-64 years	53/137	38.7	348/704	49.4	35%	(6 to 56)	18%	(-26 to 47)
≥65 years	9/30	30.0	188/325	57.9	69%	(30 to 86)	66%	(12 to 87)
LAIV4 only								
Overall	21/366	5.7	107/2165	4.9	-17%	(-89 to 28)	-22%	(-110 to 29)
2 years - 17 years	20/152	13.2	101/1043	9.7	-41%	(-136 to 15)	-19%	(-113 to 33)
2 years - 8 years	17/109	15.6	63/588	10.7	-54%	(-175 to 14)	-33%	(-161 to 32)
Influenza A(H3N2)‡								
Any vaccine								
Overall	30/72	41.7	2346/4551	51.6	33%	(-8 to 58)	43%	(4 to 66)
6 months - 17 years	1/12	8.3	668/1507	44.3	89%	(11 to 99)	90%	(14 to 99)
≥18 years	29/60	48.3	1678/3044	55.1	24%	(-27 to 54)	25%	(-31 to 57)
Influenza A(H3N2) clade 3C.2a								
Any vaccine								
Overall	9/26	34.6	2346/4551	51.6	50%	(-12 to 78)	58%	(-2 to 82)
Influenza A(H3N2) clade 3C.3a								

Any vaccine

Overall	13/33	39.4	2346/4551	51.6	39%	(-23 to 70)	52%	(-4 to 78)

Influenza B

Any vaccine

Overall	150/456	32.9	2902/5570	52.1	55%	(45 to 63)	55%	(44 to 64)
6 months - 8 years	29/89	32.6	630/1272	49.5	51%	(22 to 69)	50%	(17 to 70)
2-8 years	28/84	33.3	436/961	45.4	40%	(4 to 62)	43%	(5 to 66)
2-17 years	50/191	26.2	713/1655	43.1	53%	(34 to 67)	48%	(25 to 64)
9-17 years	22/107	20.6	277/694	39.9	61%	(36 to 76)	53%	(19 to 73)
18-49 years	31/145	21.4	841/1957	43.0	64%	(46 to 76)	68%	(51 to 79)
50-64 years	32/73	43.8	562/918	61.2	51%	(20 to 69)	48%	(14 to 69)
≥65 years	36/42	85.7	592/729	81.2	-39%	(-236 to 43)	-34%	(-236 to 47)

Any IIV

Overall	134/440	30.5	2779/5447	51.0	58%	(48 to 66)	58%	(47 to 67)
6 months - 8 years	21/81	25.9	564/1206	46.7	60%	(34 to 76)	54%	(20 to 74)
2-8 years	20/76	26.3	370/895	41.3	49%	(14 to 70)	46%	(5 to 70)
2-17 years	35/176	19.9	609/1551	39.3	62%	(44 to 74)	54%	(31 to 69)
9-17 years	15/100	15.0	239/656	36.4	69%	(45 to 83)	61%	(28 to 79)
18-49 years	30/144	20.8	822/1938	42.4	64%	(46 to 76)	69%	(52 to 80)
50-64 years	32/73	43.8	562/918	61.2	51%	(20 to 69)	48%	(14 to 69)
≥65 years	36/42	85.7	592/729	81.2	-39%	(-236 to 43)	-34%	(-236 to 47)

IIV3 only

Overall	37/343	10.8	850/3518	24.2	62%	(46 to 73)	17%	(-31 to 47)
6 months - 17 years	4/149	2.7	218/1277	17.1	87%	(63 to 95)	-4%	(-248 to 69)
18-49 years	5/119	4.2	149/1265	11.8	67%	(18 to 87)	31%	(-83 to 74)
50-64 years	7/48	14.6	121/477	25.4	50%	(-15 to 78)	-17%	(-210 to 56)
≥65 years	21/27	77.8	362/499	72.6	-32%	(-235 to 48)	-55%	(-317 to 42)

IIV3 SD only								
Overall								
≥65 years	5/11	45.5	186/323	57.6	39%	(-105 to 82)	4%	(-344 to 79)
IIV3 HD only								
≥65 years	16/22	72.7	176/313	56.2	-108%	(-445 to 21)	-92%	(-459 to 34)
IIV4 only								
Overall	81/387	20.9	1628/4296	37.9	57%	(44 to 66)	63%	(51 to 71)
6 months - 8 years	18/78	23.1	399/1041	38.3	52%	(17 to 72)	58%	(25 to 77)
9-17 years	12/97	12.4	158/575	27.5	63%	(30 to 80)	67%	(34 to 83)
18-49 years	19/133	14.3	535/1651	32.4	65%	(43 to 79)	73%	(55 to 84)
50-64 years	20/61	32.8	348/704	49.4	50%	(13 to 71)	52%	(13 to 74)
≥65 years	12/18	66.7	188/325	57.9	-46%	(-298 to 47)	-14%	(-243 to 62)
LAIV4 only								
Overall 2–49 years	16/271	5.9	107/2165	4.9	-21%	(-107 to 30)	20%	(-46 to 56)
2 years - 17 years	15/156	9.6	101/1043	9.7	1%	(-76 to 44)	18%	(-52 to 56)
2 years - 8 years	8/64	12.5	63/588	10.7	-19%	(-161 to 46)	26%	(-78 to 69)
9-17 years	7/92	7.6	38/455	8.4	10%	(-109 to 61)	15%	(-121 to 67)
Influenza B/Victoria§								
Any vaccine	59/200	29.5	2902/5570	52.1	62%	(48 to 72)	49%	(30 to 64)
Any IIV	52/193	26.9	2779/5447	51.0	65%	(51 to 74)	52%	(32 to 66)
IIV3 only	14/155	9.0	366/2571	14.2	40%	(-5 to 66)	-99%	(-311 to 4)
IIV3 HD only, ≥65 years	7/8	87.5	170/279	60.9	-349%	(-3598 to 46)	-284%	(-3701 to 61)
IIV4 only	36/177	20.3	1600/3805	42.1	65%	(49 to 76)	57%	(36 to 71)
LAIV4 only	7/139	5.0	94/1791	5.3	4%	(-111 to 56)	30%	(-62 to 69)
Influenza B/Yamagata								

					Unadjusted VE		Adjusted VE*	
Any vaccine	91/253	36.0	2902/5570	52.1	48%	(33 to 60)	57%	(42 to 67)
Any IIV	82/244	33.6	2779/5447	51.0	51%	(36 to 63)	60%	(47 to 71)
IIV3 only	23/185	12.4	850/3518	24.2	55%	(31 to 71)	41%	(-2 to 66)
IIV3 HD only, ≥65 years	9/14	64.3	176/313	56.2	-40%	(-328 to 54)	-37%	(-389 to 62)
IIV4 only	45/207	21.7	1628/4296	37.9	54%	(36 to 67)	66%	(51 to 76)
LAIV4 only	9/130	6.9	107/2165	4.9	-43%	(-190 to 29)	-9%	(-136 to 50)

*Adjusted model includes Network site, age (tail-restricted cubic spline for all age group analyses, linear within age groups), calendar time (2-week intervals), and any high-risk code in prior year

†Adults aged ≥50 years with unknown vaccine type are assumed to be IIV and are excluded from IIV3 SD, IIV3 HD, and IIV4 analyses

‡All Wisconsin enrollees were excluded from A(H3N2) analyses as there were no A(H3N2) cases at the Wisconsin site

§Wisconsin had only one case of B/Victoria, of unknown vaccine type. Wisconsin was included in the any vaccine analyses but not the others

Supplemental Table 3

Sensitivity analyses for estimated influenza vaccine effectiveness against any influenza, overall and stratified by age group and vaccine type

Age group/Vaccine type	Influenza Positive No. vaccinated/Total	(%)	Influenza Negative No. vaccinated/Total	(%)	Vaccine effectiveness Unadjusted (%)	Unadjusted (95% CI)	Adjusted* VE %	Adjusted* 95% CI
1. Include partially vaccinated children aged <9 years								
Any vaccine								
Overall	516/1331	38.8	3040/5708	53.3	44	(37 to 51)	48	(41 to 55)
6 months - 8 years	109/276	39.5	768/1410	54.5	45	(29 to 58)	49	(32 to 62)
2 years - 8 years	87/240	36.3	510/1035	49.3	41	(22 to 56)	50	(31 to 63)
2 years - 17 years	120/404	29.7	787/1729	45.5	49	(36 to 60)	53	(40 to 64)
Any IIV								
Overall	475/1290	36.8	2907/5575	52.1	47	(39 to 53)	51	(44 to 57)
2 years - 8 years	59/212	27.8	434/959	45.3	53	(35 to 66)	57	(39 to 70)
2 years - 17 years	82/366	22.4	673/1615	41.7	60	(47 to 69)	61	(48 to 71)
LAIV4								
Overall	40/677	5.9	117/2175	5.4	-10	(-60 to 24)	7	(-39 to 38)
2 years - 8 years	28/181	15.5	73/598	12.2	-32	(-111 to 18)	9	(-55 to 46)
2 years - 17 years	38/322	11.8	111/1053	10.5	-14	(-68 to 23)	9	(-39 to 41)
2. Restrict to those enrolled <5 days after illness onset								
Any vaccine								
Overall	376/1041	36.1	1915/3716	51.5	47	(39 to 54)	51	(43 to 59)
6 months - 8 years	62/187	33.2	479/951	50.4	51	(32 to 65)	56	(36 to 69)
9-17 years	30/142	21.1	215/530	40.6	61	(39 to 75)	58	(32 to 74)

18-49 years	124/421	29.5	559/1311	42.6	44	(29 to 56)	49	(34 to 61)
50-64 years	113/219	51.6	326/527	61.9	34	(10 to 52)	32	(4 to 52)
≥65 years	47/72	65.3	336/397	84.6	66	(40 to 80)	69	(42 to 83)
3. Use self-reported vaccination status only†								
Any vaccine								
Overall	442/1090	40.6	2521/4495	56.1	47	(39 to 53)	50	(42 to 57)
6 months - 8 years	99/212	46.7	593/1010	58.7	38	(17 to 54)	44	(23 to 60)
9-17 years	35/142	24.7	223/516	43.2	57	(35 to 72)	57	(33 to 73)
18-49 years	128/423	30.3	762/1646	46.3	50	(37 to 60)	55	(43 to 65)
50-64 years	116/227	51.1	473/755	62.7	38	(16 to 54)	36	(11 to 53)
≥65 years	64/86	74.4	470/568	82.8	39	(-3 to 64)	38	(-11 to 65)
4. Use EMR-confirmed vaccination status only								
Any vaccine								
Overall	459/1311	35	2714/5580	48.6	43	(36 to 50)	46	(38 to 53)
6 months - 8 years	87/254	34.3	630/1272	49.5	47	(30 to 60)	51	(33 to 64)
9-17 years	33/164	20.1	271/695	39	61	(41 to 74)	57	(33 to 72)
18-49 years	126/500	25.2	741/1961	37.8	45	(31 to 56)	50	(37 to 61)
50-64 years	136/283	48.1	501/920	54.5	23	(-1 to 41)	19	(-7 to 39)
≥65 years	77/110	70	571/732	78	34	(-3 to 58)	34	(-5 to 59)
5. Comparison-adjusted model‡								
Any vaccine								
Overall	494/1309	37.7	2902/5570	52.1	na§	na	48	(40 to 54)
6 months - 8 years	87/254	34.3	630/1272	49.5	na	na	51	(33 to 64)
2-8 years	75/228	32.9	436/961	45.4	na	na	48	(27 to 63)
2-17 years	108/392	27.6	713/1655	43.1	na	na	52	(38 to 63)
9-17 years	33/164	20.1	277/694	39.9	na	na	60	(37 to 74)
18-49 years	146/499	29.3	841/1957	43.0	na	na	49	(35 to 60)
50-64 years	150/283	53.0	562/918	61.2	na	na	24	(-1 to 43)

≥65 years	78/109	71.6	592/729	81.2	na	na	41	(4 to 64)

6. Including influenza-negative subjects enrolled outside periods of local influenza circulation								
Any vaccine								
Overall	494/1309	37.7	3076/5991	51.3	43	(35 to 49)	48	(41 to 55)

*Adjusted model includes site, age (tail-restricted cubic spline for all age group analyses, linear within age groups), calendar time (2-week intervals), and any high-risk code in prior year

†Excludes Wisconsin enrollees, for whom vaccine status was determined solely from EIR data

‡Comparison adjusted model includes site, age (spline for all ages, years for age groups), race/Hispanic ethnicity, interval from onset to enrollment, sex, general self-rated health status, calendar time (2-week intervals), and any high-risk code in the year prior to enrollment

§na = not applicable